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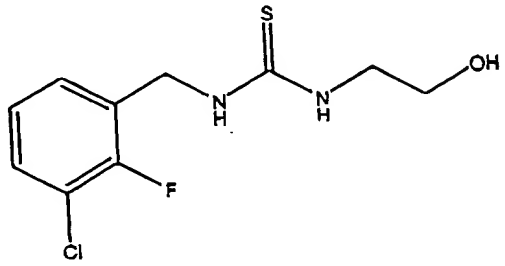
70. (New) An agent comprising:

a therapeutic component, and

a targeting component coupled to the therapeutic component, the targeting component being represented by the formula:



V.

71. (New) An agent comprising:

a therapeutic component, and

a targeting component coupled to the therapeutic component, the targeting component comprising an antibody raised from an antigen component comprising a second extracellular loop, the second extracellular loop comprising an amino acid sequence of KGDQGPQPRGRPQCKLNQE (SEQ ID NO: 1).

Remarks

This is in response to the Examiner's communication mailed July 10, 2002. A response is due October 10, 2002. Accordingly, this response is being timely filed.

Claims 1-67 were pending. By way of this response, claims 22, 29, and 45-67 have been canceled, claims 1 and 39 have been amended, and claims 68-71 have been added. Accordingly, claims 1-21, 23-28, 30-44, and 68-71 remain pending.

Applicant acknowledges that claims 22 and 29 are free from the prior art, and that these claims have only been rejected under 35 U.S.C. § 112. Applicant addresses those rejections herein.

Item 2 of the Office Action - Rejections Under 35 U.S.C. § 112, first paragraph

Claims 1-17, 22, 25-34, 36-44 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabling any targeting component that selectively binds at the alpha-2B or alpha-2B/alpha-2C adrenergic receptor subtypes as compared to the alpha-2A adrenergic receptor subtype.

Regarding the rejection of claims 22 and 29, applicant respectfully traverses the rejection. Claim 22 recites that the targeting component is a specific compound represented by Formula V of the instant application. As indicated in applicant's previous response, the compound of Formula V was the elected species for which examination was requested. The specification clearly provides a written description to enable one of ordinary skill in the art to make and use an agent comprising the compound recited in claim 22 using the disclosure of the specification and the knowledge available in the art. In fact, the Examiner has stated that the specification is enabling for an agent comprising a targeting component of formulae I-VII. Claim 29 recites that the agent has a targeting component that comprises an antibody raised from an antigen component that comprises the amino acid sequence of SEQ ID NO: 1. The specification contains a sufficient written description to

enable one of ordinary skill in the art to make and use an agent that has the claimed targeting component. Accordingly, the rejections of claims 22 and 29 should be withdrawn. For purposes of convenience, claims 22 and 29 have been rewritten as independent claims 70 and 71, respectively, and claims 22 and 29 have been canceled. Therefore, applicant submits that claims 70 and 71 are free from the art and satisfy the requirements of 35 U.S.C. § 112, first paragraph.

Applicant has also amended the claims to make more clear that the targeting component is a ligand for the alpha-2B or alpha-2B/alpha-2C adrenergic receptor subtypes. As understood by persons of ordinary skill in the art, the term "ligand" refers to a molecule or moiety that binds to a receptor to initiate or block a response. Ligands may be agonists or antagonists, and may be small natural or synthetic molecules or may be large proteins or protein-nucleic acid complexes.

Applicant respectfully traverses the rejections as they apply to the amended claims. It appears that the rejection is based on the Examiner's opinion that it would require undue experimentation to prepare an agent as recited in the claims "to determine the ones that would be used to selectively bind at the alpha-2B or alpha-2B/alpha-2C adrenergic receptor subtypes" (Office Action, page 3, last paragraph). The Examiner believes "that one of ordinary skill in the art would not know how to make any components that comprise the components as broadly defined, and how to determine that such a compound would satisfactorily selectively bind at the alpha-2B or alpha-2B/alpha-2C adrenergic receptor subtypes".

Applicant respectfully disagrees, and respectfully submits that any additional experimentation needed to practice the claimed invention would be routine, and would not be undue. Additional factors, to those identified in the Office Action, that must be taken into consideration when evaluating whether a specification enables a claim include (i) the nature of the invention; (ii) the state of the prior art; and (iii) the relative skill of those in the art.

Under 35 U.S.C. § 112, first paragraph, applicants need only provide enough information to one of ordinary skill in the art to practice the invention as claimed. *In re Eynde*, 480 F.2d 1364, 178 U.S.P.Q. 470 (C.C.P.A. 1973) ("That statutory requirement is fulfilled where one possessed of the knowledge had by one skilled in the art could use the invention given the specification disclosure without undue experimentation."). Furthermore, while "the scope of enablement varies inversely with the degree of unpredictability involved," applicant does not have to disclose an example of every species covered by a claim. *In re Angstadt*, 537 F.2d 498, 502-503, 190 U.S.P.Q. 214 (C.C.P.A. 1976). "It is not necessary that patent applicant test all embodiments of his invention; what is necessary is that he provide disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of his claims." *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200 (1991).

The requirements of 35 U.S.C. § 112, first paragraph are fulfilled where one skilled in the art could make and use the

invention given the specification disclosure without undue experimentation.

The determination of what constitutes undue experimentation in a given case requires "the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art" *Ansul Co. v. Uniroyal, Inc.*, 448 F.2d 872, 169 USPQ 759 (2d. Cir. 1961), cert. denied, 404 U.S. 1018, 172 USPQ 257 (1972)).

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention (*Ex parte Forman*, et al. 230 USPQ 546, 547 (BPAI 1986)). "The enablement requirement is met if the description enables any mode of making and using the claimed invention." *Engel Indus., Inc. v. Lockformer Co.*, 946 F.2d 1528, 1533 (Fed.Cir.1991).

Applicant has invented various agents which use different classes of molecules, such as clostridial neurotoxins, saporin, tetrodotoxin, as therapeutic components, and various classes of molecules as targeting components. In addition, applicant has disclosed how to couple the targeting components to the therapeutic components in order to form the claimed agents. For example, page 17 and page 57, line 17 to page 61, line 11 of the specification teach how to couple the components of agents of

the invention. Furthermore, U.S. Application Serial Nos. 09/548,315; 09/003,902; and PCT Publication No. WO 98/25669 are incorporated by reference in the specification (e.g., see page 20, line 12; page 22, line 12; and page 27, line 27), and provide additional description of how to make the claimed agents. Thus, the claimed agents may be made using any of the specific methods disclosed in the instant application, or may be made using conventional chemistry techniques understood by persons of ordinary skill in the art. It is well settled that a patent application need not disclose, and preferably omits, that information which is already known to those of ordinary skill in the art. Thus, applicant respectfully submits that the specification contains a written description to enable one of ordinary skill in the art to make the claimed invention. In addition, the references indicated above also include descriptions of screening technologies the enable one of ordinary skill in the art to determine if the agents bind to the adrenergic receptors recited in the claims. Screening technologies, e.g., screening assays are conventional and widely known and used to determine selectivity properties, such as binding selectivity. Screening assays suitable for determining which agents selectively bind to the specific targets are also disclosed in the examples of the instant specification.

In view of the above, applicant respectfully submits that any experimentation that may be required to test whether an agent, as recited in the claims, binds selectively to alpha-2B or alpha-2B/alpha-2C adrenergic receptors would be routine to one of ordinary skill in the art.

Because the level of persons of ordinary skill in the art is high, for example, a person with a college degree or more likely a graduate college degree, in chemistry or biology, and because the application clearly discloses how to make and test the claimed invention, applicant respectfully submits that the specification contains a written description to enable such a person of ordinary skill in the art to practice the claimed invention.

In view of the above, applicant submits that the claims satisfy the requirements of 35 U.S.C. § 112, first paragraph, and respectfully requests that the rejection of the present claims based on this statutory provision be withdrawn.

Items 3-5 of the Office Action - Rejections Under 35 U.S.C. §§ 102/103

Claims 1-17, 25-28, 30-34, and 36-44 have been rejected under 35 U.S.C. § 102(b) as allegedly anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as allegedly obvious over Foster et al. (U.S. Patent No. 5,989,545). Applicant traverses this rejection.

As indicated above, the claims have only been amended to address the § 112 rejections, and have not been amended to overcome the prior art.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." (Emphasis added;

Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). When a reference is used to anticipate a claim and the reference is silent about the asserted inherent characteristic, extrinsic evidence may be used to fill that gap. "Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference ..." *Continental Can Co. USA Inc. v. Monsanto Co.* 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749-50 (Fed. Cir. 1991)(emphasis added). "Inherency may not be established by probabilities or possibilities." *Scaltech Inc. v. Retec/Tetra L.L.C.* 178 F.3d 1378, 1384, 51 USPQ2d 1055, 1059 (Fed. Cir. 1999)(emphasis added).

Applicant respectfully traverses the rejections under 35 U.S.C. § 102, and submits that Foster et al. does not anticipate the claimed invention because Foster et al. fails to expressly or inherently teach each and every element recited in the claims.

In addition, applicant respectfully submits that the Examiner has not established a *prima facie* case of anticipation. As indicated above, claims can be anticipated if, and only if, a single prior art reference expressly or inherently discloses each and every element recited in the claims. Applicant respectfully requests the Examiner to precisely indicate where each and every element of the pending claims is expressly or inherently disclosed in Foster et al. Applicant submits that Foster et al. does not specifically expressly or inherently disclose ligands or targeting components that bind to adrenergic receptors, or ligands or targeting components that selectively

bind to alpha-2B or alpha-2B/alpha-2C adrenergic receptors as compared to alpha-2A adrenergic receptors, as recited in the pending claims. Absent such express or inherent disclosure, Foster et al. cannot properly be used to anticipate the claimed invention, and the rejection must be withdrawn.

The Office Action states that the claims have added functions which the prior art has not analyzed, and that these added functions are presumed to be inherent in the prior art composition (Office Action, page 7, first full paragraph; emphasis added).

Applicant respectfully submits that a "presumption" of inherency is not a proper basis in rejecting the claims. Either a claimed invention is inherently disclosed by a reference, or it is not inherently disclosed by a reference. To the extent that the Examiner intended to state that the claimed invention is inherently disclosed by Foster et al., applicant reiterates that the missing elements that are not expressly disclosed by a reference, must necessarily be present in the disclosure of the reference to support an inherency rejection. *Continental Can Co. USA Inc. v. Monsanto Co.*, supra.

As discussed above, applicant submits that the Examiner has not established a *prima facie* case of inherency, and applicant respectfully requests the Examiner to specifically indicate where Foster et al. inherently discloses each and every element recited in the claims. Furthermore, the Examiner has already conceded that the agents disclosed by Foster et al. do not necessarily disclose the claimed invention by stating that "the

prior art and the instant application prepare and use composition which appeared to be identical ..." (Office Action, page 7, 2nd full paragraph; emphasis added). As indicated above, inherency cannot be based on probabilities or possibilities, and therefore, Foster et al. does not inherently disclose the claimed invention.

Furthermore, applicant respectfully disagrees with the opinion that the claims have added functions that are not analyzed by the prior art. The limitations of the binding activity of the targeting component recited in the claims are definitional of the properties of the targeting component, and are not functional characterizations of the claimed agents.

The Office Action further states that "[s]ince both the prior art and the instant application prepare and use composition [sic] which appeared to be identical for treating pain. The prior art therefore suggests that the composition [sic] therein disclosed are effective in such therapy therefore suggesting the instant application under 35 U.S.C. § 103(a)." The Examiner points to *In re Fitzgerald* (205 USPQ, page 594, 2nd column, 1st full paragraph) to support the position that the burden of proof is on the applicant to demonstrate the novelty and unobviousness of the claims.

Applicant respectfully submits that the burden of proof only shifts to the applicant after the Patent Office presents a *prima facie* case of anticipation or obviousness (*In re Rijckaert*, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993) citing *In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); emphasis ours).

As indicated above, applicant submits the Examiner has not established a *prima facie* case of anticipation/inherency, and applicant submits that the Examiner has not established a *prima facie* case of obviousness. Only after the Examiner has established a *prima facie* case does the burden shift to the applicant. Because the Examiner has not established a *prima facie* case, the burden remains with the Examiner to demonstrate that the claimed invention is anticipated or obvious over Foster et al. For example, applicant submits that Foster et al. does not specifically disclose, teach, or even suggest, and provides no motivation to, modify the agents disclosed by Foster et al. to obtain the claimed invention. As the Federal Circuit has clearly indicated, "[a]lthough a reference need not expressly teach that the disclosure contained therein should be combined with another, the showing of combinability, in whatever form, must nevertheless be clear and particular." (*In re Dembiscak*, 175 F.3d 994, 999 (CAFC) 1999) emphasis ours). Absent such a clear and particular showing, the rejections cannot be maintained, and must be withdrawn.

In view of the above, applicant submits that the present claims 1-17, 25-28, 30-34, and 36-44 are not anticipated by, and are not rendered obvious over, Foster et al. under 35 U.S.C. §§ 102(b) and 103(a).

In addition, each of the present dependent claims is separately patentable over the prior art. For example, none of the prior art disclose, teach, or even suggest the present agents and methods for making the agents including the

additional feature or features recited in any of the present dependent claims. Therefore, applicant submits that each of the present claims is separately patentable over the prior art.

In conclusion, applicant has shown that the present claims satisfy the requirements of 35 U.S.C. § 112, and are not anticipated by and are unobvious from and patentable over the prior art under 35 U.S.C. §§ 102 and 103. Therefore, applicant submits that the present claims, that is claims 1-21, 23-28, 30-44, and 68-71 are allowable. Applicant requests the Examiner to pass the above-identified application to issuance at an early date. Should any matters remain unresolved, the Examiner is requested to call (collect) applicant's attorney at the telephone number given below.

Respectfully submitted,

Date: October 10, 2002

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I hereby certify that this correspondence is being transmitted via facsimile to the Commissioner for Patents in Washington, DC 20231, to fax number 703-305-3014 (GAU 1637), on or before: _____

_____
Andrea Uxa

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claim 22, 29, and 45-67 have been canceled.

Claims 1 and 39 have been amended as follows:

1. (Amended) An agent comprising:

a therapeutic component, and

a targeting ligand coupled to the therapeutic component, the targeting ligand being effective to bind to the alpha-2B or alpha-2B/alpha-2C adrenergic receptor subtype(s).

[a targeting component,

wherein the targeting component selectively binds at the alpha-2B or alpha-2B/alpha-2C adrenergic receptor subtype(s) as compared to the alpha-2A adrenergic receptor subtype.]

39. (Amended) A method for making an agent for treating pain comprising the step of producing a polypeptide from a gene having codes for at least one component of the agent, wherein the agent comprises

a therapeutic component, and

a targeting ligand coupled to the therapeutic component, the targeting ligand being effective to bind to the alpha-2B or alpha-2B/alpha-2C adrenergic receptor subtype(s).

[a targeting component,

wherein the targeting component selectively binds at the alpha-2B or alpha-2B/alpha-2C adrenergic receptor subtype(s) as compared to the alpha-2A adrenergic receptor subtype.]

The following claims have been added:

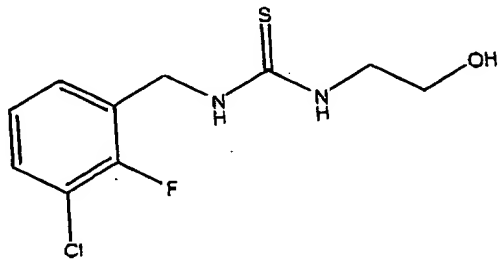
68. (New) The agent of claim 1, wherein the targeting ligand selectively binds to the alpha-2B or alpha-2B/alpha-2C adrenergic receptor subtype(s) as compared to the alpha-2A adrenergic receptor subtype.

69. (New) The method of claim 39, wherein the targeting ligand of the agent selectively binds to the alpha-2B or alpha-2B/alpha-2C adrenergic receptor subtype(s) as compared to the alpha-2A adrenergic receptor subtype.

70. (New) An agent comprising:

a therapeutic component, and

a targeting component coupled to the therapeutic component, the targeting component being represented by the formula:



V.

71. (New) An agent comprising:

a therapeutic component, and

a targeting component coupled to the therapeutic component, the targeting component comprising an antibody raised from an antigen component comprising a second extracellular loop, the

second extracellular loop comprising an amino acid sequence of KGDQGPQPRGRPQCKLNQE (SEQ ID NO: 1).